**MDNA57: A Fully Human Empowered Cytokine™ For Solid Tumors**

**PROGRAM OVERVIEW**

- Medicenna is developing a pipeline of engineered cytokine products (Superkines and Empowered Cytokines), with pharmacologically-optimized receptor-binding properties.
- MDNA57 is a fully human protein composed of a targeting cytokine fused to a pro-apoptotic payload.
- The targeting cytokine is an engineered IL-13 cytokine antagonist (MDNA413 Superkine) with biased affinity towards Type II IL4/IL13 receptors expressed in multiple solid tumors and the tumor microenvironment.
- The pro-apoptotic payload is a human BAD toxin to stimulate targeted cell death.

MDNA57 is a fully human first-in-class Superkine fusion with decreased immunogenicity for the treatment of IL-4 receptor expressing solid tumors and severe fibrotic diseases such as IPF.

**TYPE II IL4/IL13 RECEPTORS**

<table>
<thead>
<tr>
<th>IL-4 Function</th>
<th>IL-13 Function</th>
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</thead>
<tbody>
<tr>
<td>Th2 response regulator and some effector function</td>
<td>Th2 response effector cell activation</td>
</tr>
<tr>
<td>Naïve T cells</td>
<td>Smooth muscle cells</td>
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<tr>
<td>CD4 T cells</td>
<td>Epithelial cells</td>
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<tr>
<td>B cells</td>
<td>Goblet cells</td>
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<tr>
<td>Eosinophils</td>
<td>Fibroblasts</td>
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<td></td>
<td>Macrophages</td>
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<td>Dendritic cells</td>
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**DEVELOPMENT OF MDNA57**

- The MDNA413 targeting domain was generated from yeast display screening of a large number of mutations at key sites required for IL-13 binding to IL13Rα1, IL13Rα2, and IL4Rα, leading to the identification of mutations that improve binding to type II receptors.
- The BAD payload is a fully human pro-apoptotic protein engineered for increased potency.
- Compared to WT IL-13, MDNA57 has enhanced affinity for IL13Rα1 (52X lower K_D), and greatly decreased affinity towards IL13Rα2 (391X higher K_D).
- In vitro characterization of the engineered IL-13 has demonstrated its potent IL4/IL13 inhibitor properties.
- These binding properties are key to improving the safety profile and dosing parameters of MDNA57 as a second generation MDNA55.

**MDNA57 TARGET DISEASED CELLS**

- IL4-BAD fusions have been shown to elicit targeted cell killing dependent on IL4R binding, and in vivo cancer killing in mouse xenograft models.
- MDNA57 is being investigated in a sponsored research agreement with Dr Michael Rosenblum at the MD Anderson Cancer Center, where its efficacy in multiple cancer models is being demonstrated.
- MDNA57 will also be investigated for its ability to kill excess fibroblasts in fibrotic indications such as IPF to slow the progression of fibrosis in these diseases.

Medicenna is planning to develop MDNA57 in multiple tumor types expressing IL4R Type II and in IPF to clear excess fibrosis.
MDNA413: An IL-13 Superkine™ Antagonist of IL-4 and IL-13 Mediated Diseases

OPPORTUNITY OVERVIEW

• Medicenna is developing a pipeline of Superkines, engineered cytokine products (Superkines and Empowered Cytokines) with pharmacologically-optimized receptor-binding properties.

• MDNA413 is an IL-13 cytokine variant with increased affinity towards the IL13Rα1 receptor expressed on numerous effector cell types involved in Th2 responses.

• MDNA413 antagonizes IL4 and IL13 signaling to block Th2 responses and stop the effect of immune cells in inflammation and fibrosis, and to inhibit a range of tumor growth.

MDNA413 is an attractive novel biologic to address a multitude of inflammatory diseases, fibrotic indications and cancers.

DEVELOPMENT OF MDNA413

• MDNA413 was generated from yeast display screening of a large number of mutations at key sites required for IL-13 binding to IL13Ra1, IL13Ra2, and IL4Ra.

• Compared to WT IL13, MDNA413 has enhanced affinity for IL13Ra1 (52X lower K_D) and greatly decreased affinity towards IL13Ra2 (391X higher K_D), but does not bind IL4Ra1.

• In vitro characterization and exploratory in vivo studies have demonstrated that MDNA413 is a potent IL4/IL13 inhibitor through type II receptors.

INHIBITING IL4/IL13 IN MULTIPLE DISEASES

• Type II receptor activity is one of the main factors in Th2 mediated inflammatory diseases, in which IL-4 and IL-13 orchestrate effector cells that lead to disease symptoms and progression.

• IL4/IL13 play a key role in atopic dermatitis, stimulating the immune response in AD lesions, destabilizing the skin barrier and enabling infections through decreased antimicrobial peptide expression.

• Dupilumab (Dupixent) is a soon-to-be-approved IL4/IL13 antibody antagonist validating this signaling axis in atopic dermatitis.

• Signaling through Type II receptors on lung effector cells, but not Type I receptors is considered a main pathological driver of idiopathic pulmonary fibrosis.

• The small size of MDNA413 (~16 kDa) enables multiple formulation types and improved bioavailability, which unlocks a range of product development opportunities in these diseases (e.g. topical, inhaled, ...).

Medicenna is planning to develop MDNA413 in atopic dermatitis, asthma, idiopathic pulmonary fibrosis and solid tumors.